## REMARKS

Claims 1, 4-7, 25, 27 and 29 were objected to as claiming matter which was nonelected in response to a Restriction Requirement. The claims have been amended or canceled so that they refer only to the elected SEQ ID NO:2 (human MiRP1). Applicants note the Examiner's reference to the Declaration and Oath of inventor Mark T. Keating being defective and will prepare and submit a replacement Declaration and Oath. Claims 1-9 and 25-30 have also been canceled or amended to recite wildtype MiRP1 sequences and four human MiRP1 mutations that were disclosed in the specification. New claims 69-76, which are directed to nucleic acids or portions thereof of SEQ ID NO:1, nucleic acids encoding the polypeptide of SEQ ID NO:2 and mutated forms of said sequences have been added and the Specification has been amended to reflect SEQ ID NO:1. It is believed that none of these amendments constitute new matter and their entry is requested.

Claims 2, 5, and 7-9 were rejected under 35 U.S.C. § 112, first paragraph for lack of a written description. Claims 5, 7 and 9 have been amended and claims 2 and 8 have been canceled These claims are drawn to probes or primers which hybridize to a nucleic acid comprising SEQ ID NO:1 or encoding SEQ ID NO:2. Claim 9 is drawn to a primer suitable for performing a single base extension reaction across a polymorphic site, which primer hybridizes to a subsequence of SEQ ID NO:1 or the complement thereof. All primers encompassed by the claim terminate at a base immediately adjacent to and 5' from a base selected from the group consisting of nucleotide positions +22, +25, +161 and +170. The claimed primers thus encompass only wild-type sequences which abut a possibly polymorphic site, wherein each of the possible polymorphic sites has specifically been disclosed in the specification. The specification notes at page 61 that single base extension can be utilized to identify polymorphic cites immediately adjacent to the 3' end of a primer utilized in such a reaction. As recited in claim 9 such primers all terminate at a base immediately 5' of polymorphic sites that are disclosed in the specification. specifically at pages 72-73, as noted by the Examiner. It is thus submitted that the specification sufficiently describes the polymorphic site encompassed by claim 9.

In view of the amendments to the claims and above arguments, it is requested that the rejection under 35 U.S.C. 112, first paragraph for lack of written description be withdrawn.

Claims 1-9 and 24-30 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1-9 have been amended or canceled where appropriate to recite nucleic acid sequences that were disclosed in the specification. With respect to claim 5, the Examiner is of the opinion that any nucleic acid which hybridizes under stringent conditions to a nucleic acid encoding MiRP1 will not necessarily have the same biological activity as wild-type MiRP1. It is respectfully submitted that this issue is irrelevant, since the claim is to the nucleic acid, not the protein, and the nucleic acid can be used for purposes such as hybridization assays. With respect to claim 9, as noted *supra*, the specification notes the precise location of the polymorphic sites found in SEQ ID NO:1 and it is these sites that are encompassed in the claim. Claim 24 was rejected because the Examiner is of the opinion that the specification does not provide sufficient guidance for what is the starting material required for amplifying an exon of KCNE2. Claims 25, 26, 29 and 30 were rejected for encompassing gene therapy that was not enabled in the specification. It is not clear to the Applicants from the Office Action why claims 27 and 28 were rejected and it is submitted that these claims as amended are enabled by the specification, as they are directed to vectors which contain the nucleic acid sequences disclosed in the specification. Claim 24 has been canceled and claims 25-30 have been amended to recite cells transfected *in vitro* and or vectors comprising isolated nucleic acids as disclosed in the specification.

In view of the amendments to the claims and above arguments, it is requested that the rejection under 35 U.S.C. 112, first paragraph for lack of enablement be withdrawn.

Claims 1-5 and 7-9 were rejected under 35 U.S.C. 112, first paragraph as indefinite. Claims 2-4 have been canceled and it is submitted that this ground of rejection is moot for these claims. Claims 1 and 5 were rejected for the phrase "hybridizes under stringent conditions." These claims have been amended or canceled where appropriate and now recite a specific stringent hybridization condition disclosed in the application, *i.e.*, a temperature of at least 45°C with a salt concentration less than 200 mM. Claims 7-9 were rejected as being incomplete for omitting essential elements. This objection was based on the Examiner's stating that the claims are drawn to nucleic acids but refer to "SEQ ID NO:2" which is a protein sequence. Claim 7 has been amended to refer to "a nucleic acid encoding SEQ ID NO:2", claim 8 has been canceled and claim 9 has been amended to refer to SEQ ID NO:1, which is a nucleic acid sequence.

Applicants believe that the amendments to the claims obviate this rejection and its withdrawal is requested.

Claim 2 was rejected under 35 U.S.C. § 102. Claim 2 has been canceled and rewritten as new claim 77 which is believed to obviate the rejection. Withdrawal of this rejection is requested

Applicants believe that the amendments to the claims and the above comments obviate this rejection and its withdrawal is requested.

Claims 1 (based on part g), 5-7 and 25 were rejected under 35 U.S.C. § 102(b) as being anticipated by Kurtz et al. The Examiner asserts that this reference teaches a nucleic acid encoding human minK with 85% similarity that would hybridize to a nucleic acid encoding the amino acid sequence of SEQ ID NO:2 (human MiRP1). The Examiner did not include any data showing a comparison of the sequences. Attorneys for the Applicants conducted a BLAST comparison of the Kurtz nucleic acid sequence vs. SEQ ID NO:1, a copy of which is submitted with this Amendment. A BLAST comparison of the Kurtz protein vs. the protein of SEQ ID NO:2, BLAST shows 45% identity and 74% similarity across the region of amino acid residues 51-100 of SEQ ID NO:2 (the full protein is 123 amino acids).

Applicants do not understand how the Examiner obtained the numbers set forth in the Office Action and it is submitted that, based on the attached comparisons, that this ground of rejection is improper as applied to claims 1, 5-7 and 25 and its withdrawal is requested.

Claims 1 (parts g and h), 2, 5, 6 and 25-30 were rejected under 35 U.S.C. § 102(a) as being anticipated by Strausberg (GenBank Accession No. AI339609). This is a nucleic acid encoding a human minK. The Examiner asserts that this is 99.1% similar to a nucleic acid encoding SEQ ID NO:2. Applicants submit that this conclusion is incorrect. The sequence corresponds to bases 11-499 of SEQ ID NO:1 and lack sequence encoding amino acid residues 1-13 of SEQ ID NO:2. Furthermore, this reference is dated 29 December 1998. The present application was filed 14 April 2000 and claims priority to a provisional application filed 15 April 1999. Applicants have plan to submit under separate cover and at a date subsequent to this Amendment a Declaration under 37 C.F.R. 1.131 establishing a date of invention for SEQ ID NO:1 prior to November, 1998.

Applicants believe that the amendments to the claims, remarks and Declaration under 37 C.F.R. 1.131 will obviate this rejection and its withdrawal is requested.

Claims 1, 2, 5, 6 and 25-30 were rejected under 35 U.S.C. § 102(a) as being anticipated by Strausberg (GenBank Accession No. AI246239) which teaches a human MinK. The Examiner asserts that this sequence is 100 % similar to applicants' nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO:2. It appears to Applicants that this is incorrect and that the Strausberg sequence teaches only a portion of SEQ ID NO:1 of the present application, *i.e.,* bp 118-489. The start codon of SEQ ID NO:1 begins at base 74. The Strausberg sequence therefore is lacking sequence encoding the first 15 amino acid residues of SEQ ID NO:2. This reference was originally posted with a date of November 4, 1998 and was updated on January 28, 1999. Applicants submit that the above referenced Declaration to be filed under 37 C.F.R. 1.131 will establish a date of invention for SEQ ID NO:2 prior to November, 1998.

Applicants believe that the amendments to the claims, remarks and the to-be-filed Declaration under 37 C.F.R. 1.131 will obviate this rejection and its withdrawal is requested.

In view of the amendments to the claims and the above remarks, Applicants submit that the claims are fully enabled by the specification. Withdrawal of this rejection is requested.

In view of the above arguments and amendments to the claims, it is urged that all of the presently pending claims satisfy the provisions of the patent statutes. Reconsideration of this application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application.

| **RESPECTFULLY SUBMITTED,** | | | | | |
|---|---|---|---|---|---|
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Attachments: Mark-up Copy of Specification
Mark-up Copy of Claims

# Blast 2 Sequences results

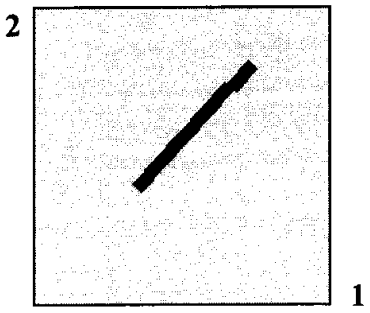


**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.1 [Aug-1-2001]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.0 wordsize: 3 Filter Align

**Sequence 1** lcl|seq_1 **Length** 132 (1 .. 132)

**Sequence 2** lcl|seq_2 **Length** 123 (1 .. 123)




NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

```
Score = 55.1 bits (131), Expect = 3e-08
Identities = 23/51 (45%), Positives = 38/51 (74%), Gaps = 1/51 (1%)

Query: 48  LYVLMVLGFFGFFTLGIMLSYIRSKKLEHSNDPFNVYIESDAWQEKDKAYV 98
           LY+++++G F F  + I++S ++SK+ EHSNDP++ YI  D WQEK K+ +
Sbjct: 51  LYLMVMIGMFSFIIVAILVSTVKSKRREHSNDPYHQYIVED-WQEKYKSQI 100

CPU time:     0.04 user secs.       0.02 sys. secs          0.06 total secs.

Gapped
Lambda      K       H
   0.318    0.134    0.395

Gapped
Lambda      K       H
   0.267   0.0410    0.140


Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Hits to DB: 128
Number of Sequences: 0
Number of extensions: 9
Number of successful extensions: 1
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's successfully gapped in prelim test: 0
Number of HSP's that attempted gapping in prelim test: 0
Number of HSP's gapped (non-prelim): 1
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length of query: 132
length of database: 240,357,305
effective HSP length: 108
effective length of query: 24
effective length of database: 43,701,401
effective search space: 1048833624
effective search space used: 1048833624
T: 9
A: 40
X1: 16 ( 7.3 bits)
X2: 129 (49.7 bits)
X3: 129 (49.7 bits)
S1: 41 (21.7 bits)
S2: 58 (26.9 bits)
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**Marked-up Copy of Specification:**

Page 73, replace with the following:

population of 1,010 individuals was also evaluated. Analysis by SSCP and DNA sequencing revealed 3 abnormalities and 1 polymorphism.

*Q9E-hMiRP1.* One of 20 patients with drug-induced arrhythmia had a C to G transversion at nucleotide +25 (nucleotide 98 of SEQ ID NO:1) of *hKCNE2* producing a Q9 to E substitution in the putative extracellular domain of hMiRP1. This mutation was not identified in 1,010 control individuals. The patient is a 76 year old African American female with a history of high blood pressure, non-insulin dependent diabetes and stroke. Two baseline electrocardiograms showed QT intervals corrected for heart rate that were borderline prolonged (QTc = 460 ms). Echocardiography revealed concentric left ventricular hypertrophy with mild to moderate diffuse hypokinesis but no ventricular dilatation. The patient was admitted to the hospital with pneumonia and treated with 7 doses of intravenous erythromycin, 500 mg every 6 hours and then switched to oral clarithromycin, 500 mg every 12 hours. After 2 doses of clarithromycin electrocardiography showed a QTc of 540 ms. The patient developed TdP and VF, requiring defibrillation. At the time, she was hypokalemic with a serum potassium level of 2.8 meq/L.

*M54T-hMiRP1.* One of 230 patients with inherited or sporadic arrhythmias had a T to C transition at nucleotide +161 (nucleotide 234 of SEQ ID NO:1) causing substitution of M54 to T in the predicted transmembrane segment. This mutation was not identified in 1,010 control individuals. This patient is a 38 year old Caucasian female who was in good health. She was on no medications. This individual had VF while jogging. Her resuscitation required defibrillation. The results from echocardiography and cardiac catheterization with electrophysiologic studies and right ventricular biopsy were normal. Subsequent electrocardiograms showed an atypical response to exercise with QTc intervals ranging from 390 to 500 ms. An automatic internal defibrillator was placed.

*I57T-hMiRP1.* Another of the 230 patients with inherited or sporadic arrhythmias had a T to C transition at +170 (nucleotide 243 of SEQ ID NO:1) causing an I57 to T substitution in the predicted transmembrane segment. This patient is a 48 year old Hispanic female who is in

good health and has no history of TdP or VF. Her resting electrocardiogram shows a prolonged QT interval (QTc = 470 ms). She is a member of a multi-generational family now under genetic, clinical and biophysical evalution.

*T8A-hMiRP1.* In 18 out of 1,260 individuals screened, an A to G polymorphism at nucleotide +22 (nucleotide 95 of SEQ ID NO:1) produced a T8 to A change in the putative extracellular domain of MiRP1. The

**Marked-up Copy of Amended Claims:**

1. An isolated [DNA] nucleic acid [comprising a nucleic acid selected from the group of:

(a) a nucleic acid comprising a nucleotide sequence] coding for a human MiRP1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2 or an isolated nucleic acid complimentary to said nucleic acid coding for a human MiRP1 polypeptide[or its complement;

(b) a nucleic acid comprising a nucleotide sequence coding for rat MiRP1 set forth in SEQ ID NO:4 or its complement;

(c) a nucleic acid comprising a nucleotide sequence coding for human MiRP2 set forth in SEQ ID NO:6 or its complement;

(d) a nucleic acid comprising a nucleotide sequence coding for mouse MiRP2 set forth in SEQ ID NO:8 or its complement;

(e) a nucleic acid comprising a nucleotide sequence coding for human MiRP3 set forth in SEQ ID NO:10 or its complement;

(f) a nucleic acid comprising a nucleotide sequence coding for mouse MiRP3 set forth in SEQ ID NO:12 or its complement;

(g) a nucleic acid which hybridizes under stringent conditions with a nucleic acid of any one of (a)-(f) and

(h) a nucleic acid which has at least 90% identity with a nucleic acid of any one of (a)-(f)].

5. (amended) An allele specific probe or primer which hybridizes to a nucleic acid encoding a polypeptide of SEQ ID NO:2 [the DNA of claim 1 or an allelic variant thereof] under stringent conditions, wherein said stringent hybridization conditions comprise a temperature of at least 45°C with a salt concentration less than 200 mM.

7. (amended) The probe or primer of claim 6 that comprises at least ten contiguous bases [from a] of nucleic acid encoding a polypeptide of SEQ ID NO:2[, 4, 6, 8, 10 or 12, or an allelic variant

thereof, or the complement of any of these] or at least ten contiguous bases of nucleic acid encoding a sequence complimentary to said nucleic acid encoding a polypeptide of SEQ ID NO:2.

9. (amended) A primer suitable for performing a single base extension reaction across a polymorphic site, which primer hybridizes to a subsequence of SEQ ID NO:[2]1 or the complement thereof, which subsequence terminates at base immediately adjacent to and 5' from a base selected from the group consisting of 22, 25, 161 or 170.

25. (amended) An *in vitro* cell transfected with the DNA of claim 1.

26. (amended) An *in vitro* cell transfected with the isolated nucleic acid of claim [2]70.

28. (amended) A vector comprising the isolated nucleic acid of claim [2]70.

29. (amended) An *in vitro* cell transfected with the vector of claim 27.

30. (amended) An *in vitro* cell transfected with the vector of claim 28.